

REMARKS

Claims 1-15 and 17-21 are pending herein. Claims 17-21 have been withdrawn from consideration.

1. The Examiner restated his previous rejections of Claims 1-15 under 35 U.S.C. §102(b) over Thulé et al. Abstracts (Diabetes, May 1999, supplement, the Abstract from meeting of June 9-13, 1999, and the Abstract from meeting of June 1998, all previously cited) as evidenced by Thulé and Liu presentations (the ADA 59th Annual Meeting, June 1999, the American Society of Gene Therapy, 2nd Annual Meeting, June 1999, and the ADA 58th Annual Meeting, June 1998, provided as References 3, 4 and 2, respectively, in the IDS filed 3/14/2006) and Vaulont et al. and Goswami et al. publications. The Examiner further noted that no new arguments regarding the rejections of claims under 35 U.S.C. §102(b) by the inventor's own publications were presented.

As the record indicates, these rejections have been extensively discussed in various prior responses, including the Request for Reconsideration filed on September 20, 2007, and the Appeal Brief filed on August 14, 2008. For the reasons discussed therein, it is respectfully submitted that Claims 1-15 are not anticipated by the Thulé et al. Abstracts, the Thulé and Liu presentations, and Vaulont and Goswami et al. publications.

The Applicant does, however, note the Examiner's statement that "[t]o the extent the Thulé (Diabetes) abstracts do not explicitly teach the actual claimed nucleotide sequences, the claims are obvious in view of the cited prior art for the following reasons." See pages 9, 11 and 13 of the Office Action dated April 2, 2009.

As discussed previously, and more extensively in the Appeal Brief, anticipation under 35 U.S.C. §102(b) requires description or enabling disclosure in a single prior art reference of each element of the claimed invention as arranged in the claim. As also extensively discussed in the Appeal Brief, the Examiner's reliance on multiple references to support anticipation rejections does not comport with the modest flexibility in the "anticipation rule". Further, the Examiner, on pages 9, 11 and 13 of the April 2, 2009 Office Action, admits that the Thulé Abstracts do not provide the actual nucleotide sequence of the promoter elements of the claimed vector. Therefore, by Examiner's own admission, a single prior art reference does not disclose the actual nucleotide sequence of the claimed construct. For this reason alone, it is respectfully submitted that the rejections of Claims 1-15 under 35 U.S.C. §102(b) over Thulé et al. Abstracts, the Thulé and Liu presentations, and Vaultont et al. and Goswami et al. publications, are improper and are respectfully requested to be withdrawn.

2. In the Office Action of April 2, 2009, the Examiner introduced three new rejections of Claims 1-15 under 35 U.S.C. §103(a) over the same Thulé et al.

Abstracts, the Thulé and Liu presentation at the ADA 59th Annual Meeting, June 1999 (provided as Reference 3 in the IDS filed 3/14/2006), and Goswami et al. and Vaultont et al. publications, and cited a new publication to Cognet et al. (J.Mol. Biol., 1987). For the reasons discussed below, these rejections are respectfully traversed.

In support of the three separate rejections of Claims 1-15 under 35 U.S.C. §103(a), over three individual Thulé et al. Abstracts, the Thulé and Liu presentation, supplemented by Vaultont et al., Goswami et al., and Cognet et al. publications, the Examiner advanced the same arguments. Therefore, for brevity and economy, only one set of arguments is provided below that applies equally to all three rejections.

A. In support of the obviousness rejection, the Examiner began his analysis with the Applicant's own invention, stating essentially that since the vector disclosed in the Thulé Abstracts "appears to be the same vector described in the specification, which would necessarily have the same structure;" the construct(s) of Claim 9 is the same as that disclosed in the Thulé Abstracts.

It is submitted that the Examiner's reliance on the Applicant's own specification in the obviousness inquiry is misplaced and improper. The Examiner's conclusion of obviousness, therefore, emanates from hindsight. The case law is legion in unequivocally stating that hindsight reconstruction of the claimed invention is improper and should be avoided. For this reason alone, it is respectfully

submitted that Claims 1-15 are not obvious over the cited references.

B. In the Office Action, the Examiner admitted that the Thulé Abstracts do not provide the actual nucleotide sequences of the elements of the claimed construct, and cited the Thulé and Liu presentation for the numerical positions of the nucleotides corresponding to the elements of the vector.

The Examiner concluded that:

[O]ne of ordinary skill in the art could use the disclosure of the Thulé abstract and presentation to know the exact nucleotide sequences needed to make the claimed vector. (Emphasis added.)

See page 10, ¶ 1, of the Office Action dated April 2, 2009.

However, it is respectfully submitted that the nucleotide numbers presented in the Thulé and Liu presentation do not exactly match with the claimed sequences.

As noted by the Examiner, the Thulé and Liu presentation slides indicate the nucleotides of the rL-PK and rIGFBP-1 to be -125 to -173 and -111 to +96, respectively. On the other hand, the sequence presented in SEQ ID No. 5 of the invention, encompasses bases best indicated by base numbers -173 to -123 and -114 to +105 for L-PK and IGFBP-1 promoters, respectively. It is well known in the biotechnology art that expression and/or functionality of a gene can be entirely affected by, for example, changing, deleting, or skipping even one base or nucleotide. In the present situation, the combined numerical differences relate not

to just one, but 15 nucleotides. Consequently, if one were to use the sequence numbering of the Thulé and Liu presentation, the resultant vector would not be the same as that claimed herein, and could even be a completely useless or non-functional sequence.

Therefore, it is respectfully submitted that if one of ordinary skill in the art were to follow the "blue print for making the claimed vector," based on the Thulé Abstracts and the Thulé and Liu presentation, it would not result in the claimed construct.

C. In the Office Action, the Examiner stated that "the actual nucleotide sequences of the rL-PK and rIGFBP-1 genes needed to make the claimed nucleotide sequence was well known in the art (see Cognet et al., Vaulont et al., and Goswami et al.)" See page 10, ¶ 1, of the Office Action dated April 2, 2009.

It is respectfully submitted that while the entire nucleotide sequences of the rL-PK and rIGFBP-1 genes were known, the precise fragments used by the present inventor to make the claimed construct, were neither taught nor suggested by Cognet et al., Vaulont et al. and Goswami et al. In other words, Vaulont et al., Goswami et al. and Cognet et al., merely disclose sequences that appear to overlap with the individual elements of the present invention. The inventor of the present invention identified and used the precise fragments in a specific order to create the claimed expressing insulin transgene which is functional, efficacious in modulating

hyperglycemia, and avoiding lethal hypoglycemia (see, for example, paragraphs [0017] to [0019], [0064] to [0079] and [0084] to [0087] and Figures 15A-15B, 23 and 26-26B, of the instant application.

In the absence of the present invention, one of ordinary skill in the art would not know which precise fragments of the rL-PK and rIGFBP-1 genes to use to make the claimed construct.

In this regard, the Examiner has previously suggested that the sequences at issue are well-known expression regulatory elements the functions of which were known. It is, however, respectfully submitted that due at least to the lack of a single, widely-accepted DNA sequence numbering methodology in the biotechnology art, one skilled in the art would not, and could not simply slice and splice native fragments from various genes - like modular mechanical units - and expect the resulting recombined sequence to function or express properly, if at all. The high unpredictability in biotechnology art would additionally be a highly discouraging factor. As the Federal Circuit has stated:

[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.¹

1. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165, 77 USPQ2d 1865, 1870 (Fed. Cir. 2006) (quotations omitted).

D. In support of the obviousness rejections, the Examiner stated that “one of ordinary skill would have been motivated to make the vector based on the teaching of the Thulé (Diabetes) abstract, and the Thulé abstract also provides evidence of an expectation of success.” See page 10, ¶ 1, of the Office Action of April 2, 2009.

As noted above, i) the Thulé et al. Abstracts did not provide the actual nucleotide sequences, ii) the nucleotide numbering disclosed in the Thulé and Liu presentation did not provide any reference for initiation of sequences, and iii) the Vaulont et al., Goswami et al., and Cognet et al. publications merely disclose longer or overlapping sequences with that disclosed in the presentation.

Given the above information and faced with the level of unpredictability and the lack of a standard base numbering technique in the relevant art, it is respectfully submitted that one of ordinary skill in the art would not have a reasonable expectation of success.

First, the nucleotide numbering disclosed in the presentation did not match with the nucleotide numbering of the vector claimed herein. Second, one faced with the longer, overlapping sequences, would not know the precise fragments to use, particularly since individual publications, although indicating a reference for initiation of sequence numbers, are inconsistent both between and within authors. See the discussion on pages 16-18 of the Appeal Brief. Third, several investigators had

attempted to utilize a native rL-PK promoter, alone or with enhancer elements, for expression in non-native environment, but had failed. See the attached Declaration of the inventor, Peter M. Thulé.

It is respectfully submitted that the failed efforts of various investigators, cited in the Declaration², establishes the unpredictability and uncertainty in the biotechnology field that would not provide the legally required reasonable expectation of success.

The Supreme Court has noted in the Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) that evidence of non-obviousness can be shown by failure of others.

In this regard, another court has held:

We can conceive no better way to determine whether an invention would have been obvious to persons of ordinary skill in the art at the time, than to see what such persons actually did or failed to do when they were confronted with the problem in the course of their work. If the evidence shows that a number of skilled technicians actually attempted, over a substantial period, to solve the specific problem which the invention overcame and failed to do so, notwithstanding the availability of all the necessary materials, it is difficult to see how a court could conclude that the invention was "obvious" to such a person at the time.³ This type of objective evidence is typically presented in declaration or affidavit form showing why one or more of these

2. Copies of the citations submitted via accompanying Fourth Supplemental Information Disclosure Statement.

3. Timely Prods. Corp. v. Stanley Arron, 523 F.2d 288, 187 USPQ 257 (2d Cir. 1975) (emphasis added).

secondary considerations supports a holding of nonobviousness.⁴ For example, the Federal Circuit has stated the usefulness of presenting secondary considerations during ex parte prosecution as follows:

[W]e hold the “secondary considerations” that the Supreme Court stated might be of possible utility in an obviousness determination, *Graham v. John Deere Co.*, ... also require a finding of nonobviousness if the matter be otherwise doubtful. In an appeal of a rejection of patent application, secondary considerations, such as commercial success, typically do not play a large part in the analysis of obviousness because the inventor usually waits until his patent issued before he swings production into full gear. Thus, a detailed analysis of secondary considerations is more common in cases like *John Deere*, which involved infringement. If, however, a patent applicant properly presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.⁵

Therefore, should any doubt remain in the Examiner’s mind of the patentability of the claimed invention, it is respectfully submitted that the attached Declaration, establishing failure of others in using precisely one of the known elements outside of the native environment, must lead to a finding of non-obviousness of Claims 1-15.

In view of the above, it is respectfully submitted that given a different nucleotide numbering in the Thulé and Liu presentation, and the longer or overlapping sequences disclosed in Vaulont et al., Goswami et al. and Cognet et al.

4. See, e.g., 37 C.F.R. §1.132.

5. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1, 7 (Fed. Cir. 1983) (emphasis added).

publications, one of ordinary skill in the art, knowing the high predictability in the biotechnology art, and that even one base or nucleotide could render the entire sequence useless, would neither be motivated to experiment with an infinite number of choices, nor arrive at what the present inventor accomplished.

For the foregoing reasons, it respectfully submitted that Claims 1-15 are not obvious over the Thulé et al. abstracts, the Thulé and Liu presentation at the ADA 59th Annual Meeting (June 1999), and Vaulont et al., Goswami et al. and Cognet et al. publications. Therefore, Claims 1-15 are allowable.

It is further respectfully requested that since Claims 1-16 are directed to a product and the non-elected Claims 17-21 are directed to the process of use, Claims 17-21 be rejoined for allowance purposes.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that all pending Claims 1-21 are in condition for allowance. Withdrawal of all the rejections and allowance of these claims are earnestly solicited.

It is believed that no additional fee is due for this submission. However, should that determination be incorrect, the Commissioner is hereby authorized to charge any deficiencies, or credit any overpayment, to our Deposit Account No. 01-0433, and notify the undersigned in due course.

Appl. No.: 09/972,916
Amdt. dated September 1, 2009
Reply to Office Action of April 2, 2009

Should the Examiner have any questions or wish to discuss further this matter, please contact the undersigned at the telephone number provided below.

Respectfully submitted,

A handwritten signature in black ink, consisting of a large, stylized 'D' followed by a series of loops and a final horizontal stroke.

DINESH AGARWAL
Attorney for Applicant(s)
Reg. No. 31,809

Law Office - Dinesh Agarwal, P.C.
5350 Shawnee Road
Suite 330
Alexandria, Virginia 22312
Telephone: (703) 642-9400
Fax: (703) 642-9402

DA/va